UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/628,472	07/31/2000	Paul K. Wolber	10003511-1	5543

22878 7590 12/24/2003

AGILENT TECHNOLOGIES, INC.
INTELLECTUAL PROPERTY ADMINISTRATION, LEGAL DEPT.
P.O. BOX 7599
M/S DL429
LOVELAND, CO 80537-0599

EXAMINER	
FORMAN, BETTY J	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 12/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/628,472	WOLBER ET AL.	
	Examiner	Art Unit	
	BJ Forman	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *16-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s)_____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 20 October 2003 has been entered.

Status of the Claims

2. This action is in response to papers filed 20 October 2003 in which claims 1 and 5 were amended. All of the amendments have been thoroughly reviewed and entered. The previous rejections in the Office Action dated 19 May 2003 are maintained. All of the arguments have been thoroughly reviewed and are discussed below.

New grounds for rejection are discussed.

Claims 1-15 are under prosecution.

Specification

3. The amendment filed 3 September 2002 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The amendments to Claims 1 and 5 (from which claims 2-4 and 6-15 depend) adds the limitation "a primer extension reaction that produces a solution phase product comprising a mixture of nucleic acids of differing sequence" but the specification as originally filed does not provide support for the new limitations. Applicant points to page 18, steps 3 and 4 for support for the new limitations. However, this merely teaches a transcription mixture is added to the hybridization chamber (step 3) and the transcription mixtures are removed and concentrated (step 4). This passage does not teach a primer extension reaction that produces a solution phase product comprising a mixture of nucleic acids of differing sequence as newly claimed. Therefore, the amendments add subject matter not supported by the original disclosure.

Applicant is required to cancel the new matter in the reply to this Office Action.

Response to Arguments

4. Applicant argues that the specification's teaching of linear PCR and SDA which do not require two primers and further teaching of in vitro transcription known to produce solution product supports the recitation "reaction that produces a solution phase product comprising a mixture of nucleic acids of differing sequence". While Applicant has provided support for single primer reactions, linear PCR, SDA and primer-less in vitro transcription, Applicant has not provided support for the claimed "solution phase product comprising a mixture of nucleic acids of differing sequence". The object over new matter is maintained.

Claim Rejections - 35 USC § 112

35 U.S.C. 112: first paragraph

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To the extent that the claimed methods are not described in the instant disclosure, claims 1-15 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

The recitation "that produces a solution phase product comprising a mixture of nucleic acids of differing sequence " is added to the newly amended independent Claims 1 and 5 (from which Claims 2-4 and 6-15 depend). However, the specification fails to define or provide any disclosure to support such claim recitation. Applicant points to page 18, steps 3 and 4 for support for the new limitations. However, this passage merely teaches a transcription mixture is added to the hybridization chamber (step 3) and the transcription mixtures are removed and concentrated (step 4). This passage does not teach a primer extension reaction that produces

a solution phase product comprising a mixture of nucleic acids of differing sequence as newly claimed. Therefore, the specification fails to support the newly added amendments.

MPEP 2163.06 notes "IF NEW MATTER IS ADDED TO THE CLAIMS, THE EXAMINER SHOULD REJECT THE CLAIMS UNDER 35 U.S.C. 112, FIRST PARAGRAPH - WRITTEN DESCRIPTION REQUIREMENT. *IN RE RASMUSSEN*, 650 F.2D 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application." MPEP 2163.06 further notes "WHEN AN AMENDMENT IS FILED IN REPLY TO AN OBJECTION OR REJECTION BASED ON 35 U.S.C. 112, FIRST PARAGRAPH, A STUDY OF THE ENTIRE APPLICATION IS OFTEN NECESSARY TO DETERMINE WHETHER OR NOT "NEW MATTER" IS INVOLVED. *APPLICANT SHOULD THEREFORE SPECIFICALLY POINT OUT THE SUPPORT FOR ANY AMENDMENTS MADE TO THE DISCLOSURE*" (emphasis added).

Response to Arguments

7. Applicant argues that the specification's teaching of linear PCR and SDA which do not require two primers and further teaching of in vitro transcription known to produce solution product supports the recitation "reaction that produces a solution phase product comprising a mixture of nucleic acids of differing sequence". While Applicant has provided support for single primer reactions, linear PCR, SDA and primer-less in vitro transcription, Applicant has not provided support for the claimed "solution phase product comprising a mixture of nucleic acids of differing sequence". The rejection over new matter is maintained.

35 U.S.C. 112: second paragraph

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 5-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 5-9 are indefinite in Claim 5 because the claim is drawn to a probe "described by the formula: surface-L-R-F-cV-5' wherein: L in an optional linking domain". Because the probe is "described" by the formula containing "L", it is unclear whether L is optional as subsequently described.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 1-15 are rejected under 35 U.S.C. 102(e) as being anticipated by Wolber et al (U.S. Patent No. 6,235,483, filed 31 January 2000).

The applied reference has a common inventor and assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Regarding Claim 1, Wolber et al disclose a method for producing a mixture of nucleic acids comprising: providing an array of distinct single-stranded probe nucleic acids of differing sequence where each distinct probe present on the array comprises a constant domain (i.e. poly A) and a complement variable domain (i.e. coding sequences); hybridizing nucleic acids complementary to the constant domain with said array of probes to produce a template array of overhang comprising duplex nucleic acids wherein each overhang comprising duplex of said array comprises a double-stranded constant region and a single-stranded variable region overhang; subjecting the array of overhang comprising duplex nucleic acids to a primer extension reaction that produces a solution phase product comprising a mixture of nucleic acids of differing sequence and separating said mixture from said template array (Columns 6 and 13).

Regarding Claim 2, Wolber et al disclose the method wherein the nucleic acid mixture comprises deoxyriobologonucleotides (Column 6).

Regarding Claim 3, Wolber et al disclose the method wherein the constant domain comprise at least one domain selected from a linker domain, a functional domain and a recognition domain (Columns 5-6).

Regarding Claim 4, Wolber et al disclose the method wherein step (c) comprises linear PCR (Column 6).

Regarding Claim 5, Wolber et al disclose a method for producing a mixture of nucleic acids comprising: providing an array of distinct single-stranded probe nucleic acids of differing

sequence where each distinct probe present on the array comprises a constant domain (i.e. constant priming sequence) and a complement variable domain (i.e. flanking sequences); hybridizing nucleic acids complementary to the constant domain with said array of probes to produce a template array of overhang comprising duplex nucleic acids wherein each overhang comprising duplex of said array comprises a double-stranded constant region and a single-stranded variable region overhang; subjecting the array of overhang comprising duplex nucleic acids to a primer extension reaction that produces a solution phase product comprising a mixture of nucleic acids of differing sequence and separating said mixture from said template array (Columns 6 and 13) wherein the probe comprises: 3' linker- recognition domain-functional domain-complement domain and the complementary nucleic acids comprise a complement of the recognition domain and complement of the functional domain (Columns 5-6)

Regarding Claim 6, Wolber et al teach the method wherein the linker domain ranges in length from about 0 to 10 bases (Columns 5-6).

Regarding Claim 7, Wolber et al teach the method wherein the functional domain is an RNA polymerase promoter domain (Column 5-6).

Regarding Claim 8, Wolber et al teach the method wherein the recognition domain is recognized by a restriction endonuclease (Column 7, lines 21-44).

Regarding Claim 9, Wolber et al teach the method the primer extension step comprises linear PCR or in vitro transcription (Columns 5-6).

Regarding Claim 10, Wolber et al disclose a method for producing a mixture of nucleic acids comprising: generating a mixture of nucleic acids according to Claim 1 and employing the mixture as primers in a target generation step whereby a population of nucleic acids is produced (Column 8).

Regarding Claim 11, Wolber et al. teach the similar method wherein the target generation step comprises template driven primer extension (Column 8).

Regarding Claim 12, Wolber et al. teach the similar method wherein said target generation step produces labeled target nucleic acids (Column 8).

Regarding Claim 13, Wolber et al. teach the similar method of generating a set of target nucleic acids according to the method of Claim 10; and further contacting said set of nucleic acids with nucleic acids under hybridizing condition; and detecting the presence of target nucleic acids hybridized to nucleic acids (Column 8).

Regarding Claim 14, Wolber et al. teach the similar method of Claim 13 wherein the nucleic acids are labeled (Column 8).

Regarding Claim 15, Wolber et al teach their method wherein following hybridization and/or detection, unbound target molecules are removed (Column 8-10).

Response to Arguments and Declaration

12. Regarding the rejection over Wolber et al: Applicant relied on the Declaration filed under 37 C.F.R. 1.132 to over come the rejection.

The Declaration filed on 18 August 2003 under 37 CFR 1.132 has been considered but is ineffective to overcome the Wolber et al reference.

The declaration states that 1) Wolber is a co-inventor of the instant application; 2) Wolber is a co-inventor of U.S. Patent No. 6,235,483; and 3) Wolber conceived and invented the subject matter disclosed but not claimed in the '483 patent that is subject of the claims of the present application.

The declaration is insufficient to overcome the above rejection for the following reason. The declaration states that "I conceived and invented the subject matter disclosed but not claimed in the cited patent". Which means that, Wolber is the inventor of the disclosed subject matter and that Wolber, Kincaid, Amorese, Ilsley, and Atwell are inventors of the instantly claimed subject matter. Therefore, according to the Declaration, the subject matter disclosed in the patent and the instantly claimed subject matter have different inventive

entities. As such, the '438 disclosure is "by another" and therefore, the rejection under 35 U.S.C. 102(e) is deemed proper and therefore maintained.

13. Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Bulyk et al (Nature Biotechnology, June 1999, 17: 573-577).

Regarding Claim 1, Bulyk et al disclose a method for producing a mixture of nucleic acids comprising: providing an array of distinct single-stranded probe nucleic acids of differing sequence where each distinct probe present on the array comprises a constant domain (i.e. constant priming sequence) and a complement variable domain (i.e. flanking sequences); hybridizing nucleic acids complementary to the constant domain with said array of probes to produce a template array of overhang comprising duplex nucleic acids wherein each overhang comprising duplex of said array comprises a double-stranded constant region and a single-stranded variable region overhang; subjecting the array of overhang comprising duplex nucleic acids to a primer extension reaction that produces a solution phase product comprising a mixture of nucleic acids of differing sequence and separating said mixture from said template array (page 576, right column-page 577, left column) wherein upon restriction digestion, the reaction products are released into solution (page 577, left column second full paragraph) and wherein double-stranded nucleic acids comprise single-stranded nucleic acids as claimed.

Regarding Claim 2, Bulyk et al disclose the method wherein the nucleic acid mixture comprises deoxyriobologonucleotides (page 573, right column first full paragraph).

Regarding Claim 3, Bulyk et al disclose the method wherein the constant domain comprise at least one domain selected from a linker domain, a functional domain and a recognition domain (page 574, Fig. 1).

Regarding Claim 4, Bulyk et al disclose the method wherein step (c) comprises linear PCR i.e. utilizes a single primer for priming only the 3' end of the immobilized nucleic acids (page 574, Fig. 1).

Response to Arguments

14. Applicant acknowledges that the method of Bulyk et al produces solution phase products (page 9, second paragraph of the After Final Response filed 15 August 2003). However, Applicant argues that the products of Bulyk et al are double stranded and not single-stranded as newly claimed. The argument has been considered but is not found persuasive because the claims are drawn to a solution phase product "comprising" a mixture of single-stranded nucleic acids. The open claim language "comprising" encompasses the second strand hybridized to the single-strand in the double-stranded product of Bulyk et al. Therefore, Bulyk et al anticipate the claims as written.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. Claims 5-6 and 8-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bulyk et al (Nature Biotechnology, June 1999, 17: 573-577).

Regarding Claim 5, Bulyk et al disclose a method for producing a mixture of nucleic acids comprising: providing an array of distinct single-stranded probe nucleic acids of differing

sequence where each distinct probe present on the array comprises a constant domain (i.e. constant priming sequence) and a complement variable domain (i.e. flanking sequences); hybridizing nucleic acids complementary to the constant domain with said array of probes to produce a template array of overhang comprising duplex nucleic acids wherein each overhang comprising duplex of said array comprises a double-stranded constant region and a single-stranded variable region overhang; subjecting the array of overhang comprising duplex nucleic acids to a primer extension reaction that produces a solution phase product comprising a mixture of nucleic acids of differing sequence and separating said mixture from said template array (page 576, right column-page 577, left column) wherein the probe comprises: 3' linker-recognition domain (constant priming sequence)-functional domain (proximal flanking sequence)-(distal flanking sequence) and the complementary nucleic acids comprise a sequence which hybridizes to the probe nucleic acid (Abstract). Bulyk et al teach their probes comprise sequences to facilitate primer binding and extension (Abstract) which clearly suggests that their probes comprise both a functional and recognition domains, but they do not specifically teach nucleic acids comprise both functional and recognition domains. However, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the functional and recognition domain suggestion of Bulyk et al the their probes of their array designed for amplification of template-specific sequences for the expected benefit of facilitating the amplification and purification of template-specific sequences as suggested by Bulyk et al (Abstract).

Regarding Claim 6, Bulyk et al teach the method wherein the linker domain ranges in length from about 0 to 10 bases i.e. HEG linker (page 574, left column, lines 1-4, Fig. 1 and page 576, right column, first full paragraph).

Regarding Claim 8, Bulyk et al teach the method wherein the recognition domain is recognized by a restriction endonuclease (page 574, left column first full paragraph).

Regarding Claim 9, Bulyk et al teach the method the primer extension step comprises in vitro transcription i.e. the functional domain provides a polymerase binding region to which the DNA polymerase binds to initiate transcription (page 575, right column, third full paragraph).

Response to Arguments

17. Applicant reiterates the argument regarding the newly claimed single-stranded nucleic acids. The argument has been considered but is not found persuasive for the reasons stated above i.e. the open claim language "comprising" encompasses a double-stranded nucleic acid.

18. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bulyk et al (Nature Biotechnology, June 1999, 17: 573-577) as applied to Claim 5 above and further in view of Dattagupta (U.S. Patent No. 5,215,899, issued 1 June 1993).

Regarding Claim 7, Regarding Claim 5, Bulyk et al disclose a method for producing a mixture of nucleic acids comprising: providing an array of distinct single-stranded probe nucleic acids of differing sequence where each distinct probe present on the array comprises a constant domain (i.e. constant priming sequence) and a complement variable domain (i.e. flanking sequences); hybridizing nucleic acids complementary to the constant domain with said array of probes to produce a template array of overhang comprising duplex nucleic acids wherein each overhang comprising duplex of said array comprises a double-stranded constant region and a single-stranded variable region overhang; subjecting the array of overhang comprising duplex nucleic acids to a primer extension reaction that produces a solution phase product comprising a mixture of nucleic acids of differing sequence and separating said mixture from said template array (page 576, right column-page 577, left column) wherein the probe comprises: 3' linker- recognition domain (constant priming sequence)-functional domain

(proximal flanking sequence)-(distal flanking sequence) and the complementary nucleic acids comprise a sequence which hybridizes to the probe nucleic acid (Abstract). Bulyk et al teach their probes comprise sequences to facilitate primer binding and extension (Abstract) which clearly suggests that their probes comprise both a functional and recognition domains, but they do not teach an RNA polymerase promoter domain. However, RNA polymerase were well know in the art at the time the claimed invention was made as taught by Dattagupta who teaches a similar method for producing a mixture of distinct deoxyribo-oligonucleotide wherein the a plurality of single-stranded probes having the formula: A-B-C-5' wherein is A recognition domain, B is functional domain and C is a variable domain. The method comprising contacting the probes with nucleic acids having the formula A' B'; and subjecting the overhang duplex to primer extension to thereby produce a plurality of nucleic acids (Column 4, lines 27-53) wherein the functional + recognition domains function to recognize the target sequence and transcription initiation site wherein the functional domain is an RNA polymerase promoter domain wherein binding of the polymerase initiates RNA transcription (Abstract) (Column 5, lines 22-27). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the polymerase of Bulyk et al with RNA polymerase taught by Dattagupta et al. whereby transcription and amplification are performed without using the time consuming and cumbersome thermocycling of PCR for the obvious benefits of simplified transcription and amplification as taught by Dattagupta et al. (Column 3, lines 58-67).

Response to Arguments

19. Applicant reiterates the argument regarding the newly claimed single-stranded nucleic acids. The argument has been considered but is not found persuasive for the reasons stated above i.e. the open claim language "comprising" encompasses a double-stranded nucleic acid.

20. Claims 10-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bulyk et al (Nature Biotechnology, June 1999, 17: 573-577) in view of Cantor et al (U.S. Patent No. 5,795,714, issued August 18, 1998).

Regarding Claim 10, Bulyk et al disclose a method for producing a mixture of nucleic acids comprising: providing an array of distinct single-stranded probe nucleic acids of differing sequence where each distinct probe present on the array comprises a constant domain (i.e. constant priming sequence) and a complement variable domain (i.e. flanking sequences); hybridizing nucleic acids complementary to the constant domain with said array of probes to produce a template array of overhang comprising duplex nucleic acids wherein each overhang comprising duplex of said array comprises a double-stranded constant region and a single-stranded variable region overhang; subjecting the array of overhang comprising duplex nucleic acids to a primer extension reaction that produces a solution phase product comprising a mixture of nucleic acids of differing sequence and separating said mixture from said template array (page 576, right column-page 577, left column) wherein the mixture of nucleic acids are used to produce a population of target molecules (page 577, left column) but they do not teach the mixture of nucleic acids are employed as primers to generate a population of target nucleic acids. However, Cantor et al. teach a similar method for producing a mixture of nucleic acids comprising: providing an array of distinct single-stranded probe nucleic acids, contacting said array with nucleic acids complementary to said constant domain under hybridization conditions whereby a template array of overhang comprising duplex nucleic acids is produced, wherein each overhang comprising duplex of said array comprises a double-stranded region and a single-stranded variable region overhang; subjecting said template array to primer extension to produce a mixture of nucleic acids (Column 13, line 41-Column 14, line 22) and further comprising; employing said mixture as primers in a target generation step in which target nucleic acids are produced i.e. to create duplicate arrays (Column 4, lines 48-50) wherein the nucleic acids are RNAs (Column 6, lines 43-47). It would have been obvious to

one of ordinary skill in the art at the time the claimed invention was made to modify the method of Bulyk et al by employing the mixture of nucleic acids as primers to thereby duplicate template arrays as taught by Cantor et al (Column 4, lines 48-65).

Regarding Claim 11, Cantor et al. teach the similar method wherein the target generation step comprises template driven primer extension (Column 4, lines 57-58).

Regarding Claim 12, Cantor et al. teach the similar method wherein said target generation step produces labeled target nucleic acids (Column 9, lines 28-50).

Regarding Claim 13, Cantor et al. teach the similar method of generating a set of target nucleic acids according to the method of Claim 10; and further contacting said set of nucleic acids with nucleic acids under hybridizing condition; and detecting the presence of target nucleic acids hybridized to nucleic acids i.e. the generated nucleic acids are free in solution and hybridized to other nucleic acids for detecting the nucleic acids (Column 4, lines 48-65). Cantor et al. do not teach the nucleic acids in solution are contacted with an array of probes. However, It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the hybridization of Cantor et al. by hybridizing the generated nucleic acids to probes on an array to thereby detect the generated sequences using positional screening for the expected benefit of rapidly and accurately the sequence of the nucleic acid generated as taught by Cantor et al. (Column 4, lines 11-15).

Regarding Claim 14, Cantor et al. teach the similar method of Claim 13 wherein the nucleic acids are labeled (Column 9, lines 1-27).

Regarding Claim 15, Bulyk et al teach their method wherein following hybridization and/or detection, unbound target molecules are removed (page 574, left column, first full paragraph). Cantor et al. teach the similar method of Claim 13 for producing a mixture of nucleic acids comprising: providing an array of distinct single-stranded probe nucleic acids, contacting said array with nucleic acids complementary to said constant domain under hybridization conditions whereby a template array of overhang comprising duplex nucleic acids

is produced, wherein each overhang comprising duplex of said array comprises a double-stranded region and a single-stranded variable region overhang; subjecting said template array to primer extension to produce a mixture of nucleic acids (Column 13, line 41-Column 14, line 22) but they do not specifically teach said method further comprises washing unbound target away from the surface of the array. However, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the know washing step to remove unbound nucleic acids to the methods of Bulyk et al and Cantor et al. washing unbound target from the surface of the array for the obvious benefit of eliminating non-specific sequences and reducing background hybridizations.

Response to Arguments

21. Applicant reiterates the argument regarding the newly claimed single-stranded nucleic acids. The argument has been considered but is not found persuasive for the reasons stated above i.e. the open claim language "comprising" encompasses a double-stranded nucleic acid.

22. Claims 1-6, 8-9 are rejected under 35 U.S.C. 103(e) as being unpatentable over Lipshutz et al (U.S. Patent No. 6,280,950 B1, filed 10 March 1997) in view of Bulyk et al (Nature Biotechnology, June 1999, 17: 573-577).

Regarding Claim 1, Lipshutz et al disclose a method for producing a mixture of nucleic acids (Column 2, lines 16-37) comprising: providing an array of distinct single-stranded probe nucleic acids of differing sequence where each distinct probe present on the array comprises a constant domain (i.e. 3' terminal sequence) and a complement variable domain (i.e. unique central sequences); hybridizing nucleic acids complementary to the constant domain (i.e.

primers) with said array of probes to produce a template array of overhang comprising duplex nucleic acids wherein each overhang comprising duplex of said array comprises a double-stranded constant region and a single-stranded variable region overhang; subjecting the array of overhang comprising duplex nucleic acids to a primer extension reaction that produces a solution phase product comprising a mixture of nucleic acids of differing sequence and separating said mixture from said template array (Column 2, lines 16-37; Column 21, line 34-Column 23, line 21; and Fig. 1). Lipshutz et al teach the method wherein the 5' sequence of the probe is common to all templates whereby the template is amplified using 5' and 3' primers. While they do not teach the 5' end is variable, Bulyk et al teach a similar method wherein the 5' sequence of the probe is variable and whereby template is amplified via primer extension using a single primer to thereby replicate templates of long length with accuracy and efficiency (Abstract and page 573, right column first full paragraph). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the 5' and 3' constant region template of Lipshutz et al with the 3' constant region and 5' variable region template of Bulyk et al wherein the template is amplified accurately and efficiently using a single primer. One of ordinary skill in the art would have been motivated to combine the teachings of Bulyk et al and Lipshutz et al based on the teachings of Bulyk et al to thereby efficiently and accurately produce the desired mixture of nucleic acids as taught by Bulyk et al (Abstract and page 573, right column first full paragraph).

Regarding Claim 2, Lipshutz et al disclose the method wherein the mixture of nucleic acids is a mixture of DNA (i.e. the primer is extended via PCR using Taq DNA polymerase, Column 22,lines 21-27).

Regarding Claim 3, Lipshutz et al disclose the method wherein the constant domain comprises at least one domain selected from the group consisting of a linker domain, a functional domain and a recognition domain (Column 16, lines 16-46 and Column 21, lines 5-22).

Regarding Claim 4, Lipshutz et al teach the method the primer extension step comprises in vitro transcription i.e. the functional domain provides a polymerase binding region to which the polymerase binds to initiate transcription (Column 15, lines 45-54)

Regarding Claim 5, Lipshutz et al teach a method for producing a mixture of a plurality of distinct deoxyribo-oligonucleotides of differing sequence wherein each oligonucleotide comprises a different variable region (Column 2, lines 16-37) comprising: providing an array of a plurality of surface immobilized single stranded probes wherein each probe on the array comprises a constant domain (i.e. 3' terminal sequence) and a complement variable domain (i.e. unique central sequences) wherein the constant domain comprises ancillary sequences (Column 11, lines 17-20); contacting the array under hybridizing conditions with a population of nucleic acids complementary to the constant domain whereby an array of overhang duplex nucleic acids is produced; subjecting the duplex nucleic acids to primer extension reaction that produces a solution phase product comprising a mixture of nucleic acids of differing sequence and separating said mixture from said template array to produce a mixture of a plurality of distinct oligonucleotides of differing sequence each comprising a different variable domain (Column 2, lines 16-37; Column 21, line 34-Column 23, line 21; and Fig. 1). Lipshutz et al teach the probes are linked to a solid support via a linker (Column 21, lines 5-8) and further comprise a constant domain (i.e. 3' terminal sequence) which comprises ancillary sequences (Column 11, lines 17-20) wherein the ancillary sequences facilitate amplification and /or purification. Specifically, their functional domains facilitate amplification (e.g. common primer binding domain; Column 15, line 35- 67) and their recognition domains facilitate purification (e.g. restriction enzyme and sequence-specific recognition domains; Column 16, lines 16-46). Lipshutz et al teach their probes comprise ancillary sequences to facilitate amplification and purification which clearly suggests that their probes comprise both a functional and recognition domains, but they do not specifically teach probes comprise both functional and recognition domains having the formula L-R+F-cV-5'. However, it would have been obvious to

one of ordinary skill in the art at the time the claimed invention was made to apply the functional and recognition domain suggestion of Lipshutz et al the their probes of their array designed for amplification of template-specific sequences for the expected benefit of facilitating the amplification and purification of template-specific sequences as suggested by Lipshutz et al (Column 11, lines 17-20).

Regarding Claim 6, Lipshutz et al teach the method wherein the linker domain ranges in length from about 0 to 10 bases e.g. terminal hydroxyl (Column 21, lines 5-15).

Regarding Claim 8, Lipshutz et al teach the method wherein the recognition domain is recognized by a restriction endonuclease (Column 16, lines 32-37).

Regarding Claim 9, Lipshutz et al teach the method the primer extension step comprises in vitro transcription i.e. the functional domain provides a polymerase binding region to which the polymerase binds to initiate transcription (Column 15, lines 45-54).

Response to Arguments

23. Applicant argues that one of ordinary skill in the art would not have been motivated to combine the teaching of Lipshutz with that of Bulyk because the method of Lipshutz requires two constant domains as primer sites. The argument has been considered but is not found persuasive because as stated in the final office action, Bulyk et al teach a method similar to that of Lipshutz wherein the 5' sequence of the probe is variable and whereby template is amplified via primer extension using a single primer to thereby replicate templates of long length with accuracy and efficiency (Abstract and page 573, right column first full paragraph). Therefore one of ordinary skill in the art would have been motivated to combine the teachings to thereby replicate templates of long length with accuracy and efficiency (Bulyk, Abstract and page 573, right column first full paragraph).

Applicant further reiterates the argument regarding the double-stranded nucleic acids products of Bulyk et al. The argument has been considered but is not found persuasive for

the reasons stated above i.e. the open claim language "comprising" encompasses a double-stranded nucleic acid.

24. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lipshutz et al (U.S. Patent No. 6,280,950 B1, filed 10 March 1997)) and Bulyk et al (Nature Biotechnology, June 1999, 17: 573-577) as applied to Claim 5 above and further in view of Dattagupta (U.S. Patent No. 5,215,899, issued 1 June 1993).

Regarding Claim 7, Lipshutz et al teach a method for producing a mixture of a plurality of distinct deoxyribo-oligonucleotides of differing sequence wherein each oligonucleotide comprises a different variable region (Column 2, lines 16-37) comprising: providing an array of a plurality of surface immobilized single stranded probes wherein each probe on the array comprises a constant domain (i.e. 3' terminal sequence) and a complement variable domain (i.e. unique central sequences) wherein the constant domain comprises ancillary sequences (Column 11, lines 17-20); contacting the array under hybridizing conditions with a population of nucleic acids complementary to the constant domain whereby an array of overhang duplex nucleic acids is produced; subjecting the duplex nucleic acids to primer extension reaction that produces a solution phase product comprising a mixture of nucleic acids of differing sequence and separating said mixture from said template array to produce a mixture of a plurality of distinct oligonucleotides of differing sequence each comprising a different variable domain (Column 2, lines 16-37; Column 21, line 34-Column 23, line 21; and Fig. 1) wherein the functional domain provides a polymerase binding region for polymerase binding and transcription initiation (Column 15, lines 45-54) but they do not teach an RNA polymerase

promoter domain. However, RNA polymerase were well know in the art at the time the claimed invention was made as taught by Dattagupta who teaches a similar method for producing a mixture of distinct deoxyribo-oligonucleotide wherein the a plurality of single-stranded probes having the formula: A-B-C-5' wherein is A recognition domain, B is functional domain and C is a variable domain. The method comprising contacting the probes with nucleic acids having the formula A' B'; and subjecting the overhang duplex to primer extension to thereby produce a plurality of nucleic acids (Column 4, lines 27-53) wherein the functional + recognition domains function to recognize the target sequence and transcription initiation site wherein the functional domain is an RNA polymerase promoter domain wherein binding of the polymerase initiates RNA transcription (Abstract) (Column 5, lines 22-27). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the polymerase of Lipshutz et al with RNA polymerase taught by Dattagupta et al. whereby transcription and amplification are performed without using the time consuming and cumbersome thermocycling of PCR for the obvious benefits of simplified transcription and amplification as taught by Dattagupta et al. (Column 3, lines 58-67).

Response to Argument

25. Applicant argues that Dattagupta et al do not cure the deficiencies of Lipshutz and Bulyk and therefore, the combination of their teachings does not obviate the instant invention. The argument has been considered but is not found persuasive for the reasons stated above regarding Lipshutz and Bulyk.

26. Claims 10-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lipshutz et al (U.S. Patent No. 6,280,950 B1, filed 10 March 1997)) in view of Bulyk et al (Nature Biotechnology, June 1999, 17: 573-577) and Cantor et al (U.S. Patent No. 5,795,714, issued August 18, 1998).

Regarding Claim 10, Lipshutz et al teach a method for producing a mixture of nucleic acids according to Claim 1 comprising: providing an array of distinct single-stranded probe nucleic acids of differing sequence where each distinct probe present on the array comprises a constant domain (i.e. 3' terminal sequence) and a complement variable domain (i.e. unique central sequences); hybridizing nucleic acids complementary to the constant domain (i.e. primers) with said array of probes to produce a template array of overhang comprising duplex nucleic acids wherein each overhang comprising duplex of said array comprises a double-stranded constant region and a single-stranded variable region overhang; subjecting the array of overhang comprising duplex nucleic acids to a primer extension reaction that produces a solution phase product comprising a mixture of nucleic acids of differing sequence and separating said mixture from said template array (Column 2, lines 16-37; Column 21, line 34-Column 23, line 21; and Fig. 1) wherein the mixture of nucleic acids are used to produce a population of target molecules (Column 9, line 30-41). Lipshutz et al teach the method wherein the 5' sequence of the probe is common to all templates whereby the template is amplified using 5' and 3' primers. While they do not teach the 5' end is variable, Bulyk et al teach a similar method wherein the 5' sequence of the probe is variable and whereby template is amplified via primer extension using a single primer to thereby replicate templates of long length with accuracy and efficiency (Abstract and page 573, right column first full paragraph). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the 5' and 3' constant region template of Lipshutz et al with the 3' constant region and 5' variable region template of Bulyk et al wherein the template is amplified accurately and efficiently using a single primer. One of ordinary skill in the art would have

been motivated to combine the teachings of Bulyk et al and Lipshutz et al based on the teachings of Bulyk et al to thereby efficiently and accurately produce the desired mixture of nucleic acids as taught by Bulyk et al (Abstract and page 573, right column first full paragraph).

Lipshutz et al do not teach the mixture of nucleic acids are employed as primers to generate the population. However, Cantor et al. teach a similar method for producing a mixture of nucleic acids comprising: providing an array of distinct single-stranded probe nucleic acids, contacting said array with nucleic acids complementary to said constant domain under hybridization conditions whereby a template array of overhang comprising duplex nucleic acids is produced, wherein each overhang comprising duplex of said array comprises a double-stranded region and a single-stranded variable region overhang; subjecting said template array to primer extension to produce a mixture of nucleic acids (Column 13, line 41-Column 14, line 22) and further comprising; employing said mixture as primers in a target generation step in which target nucleic acids are produced i.e. to create duplicate arrays (Column 4, lines 48-50) wherein the nucleic acids are RNAs (Column 6, lines 43-47). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Lipshutz et al by employing the mixture of nucleic acids as primers to thereby duplicate template arrays as taught by Cantor et al (Column 4, lines 48-65).

Regarding Claim 11, Cantor et al. teach the similar method wherein the target generation step comprises template driven primer extension (Column 4, lines 57-58).

Regarding Claim 12, Cantor et al. teach the similar method wherein said target generation step produces labeled target nucleic acids (Column 9, lines 28-50).

Regarding Claim 13, Cantor et al. teach the similar method of generating a set of target nucleic acids according to the method of Claim 10; and further contacting said set of nucleic acids with nucleic acids under hybridizing condition; and detecting the presence of target

nucleic acids hybridized to nucleic acids i.e. the generated nucleic acids are free in solution and hybridized to other nucleic acids for detecting the nucleic acids (Column 4, lines 48-65). Cantor et al. do not teach the nucleic acids in solution are contacted with an array of probes. However, It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the hybridization of Cantor et al. by hybridizing the generated nucleic acids to probes on an array to thereby detect the generated sequences using positional screening for the expected benefit of rapidly and accurately the sequence of the nucleic acid generated as taught by Cantor et al. (Column 4, lines 11-15).

Regarding Claim 14, Cantor et al. teach the similar method of Claim 13 wherein the nucleic acids are labeled (Column 9, lines 1-27).

Regarding Claim 15, Lipshutz et al teach their method wherein following hybridization and/or detection, unbound target molecules are removed by washing (e.g. Column 9 and 36-39). Cantor et al. teach the similar method of Claim 13 for producing a mixture of nucleic acids comprising: providing an array of distinct single-stranded probe nucleic acids, contacting said array with nucleic acids complementary to said constant domain under hybridization conditions whereby a template array of overhang comprising duplex nucleic acids is produced, wherein each overhang comprising duplex of said array comprises a double-stranded region and a single-stranded variable region overhang; subjecting said template array to primer extension to produce a mixture of nucleic acids (Column 13, line 41-Column 14, line 22) but they do not specifically teach said method further comprises washing unbound target away from the surface of the array. However, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the know washing step to remove unbound nucleic acids to the methods of Lipshutz et al and Cantor et al. washing unbound target from the surface of the array for the obvious benefit of eliminating non-specific sequences and reducing background hybridizations.

Response to Argument

27. Applicant argues that Cantor et al do not cure the deficiencies of Lipshutz and Bulyk and therefore, the combination of their teachings does not obviate the instant invention. The argument has been considered but is not found persuasive for the reasons stated above regarding Lipshutz and Bulyk.

Prior Art

28. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Uhlen (U.S. Patent No. 5,405,746, issued 11 April 1995) teach a method for producing nucleic acids comprising primers having constant and variable domains, extending the primers and separating the nucleic acids (Column 6, line 42-Column 7, line 25 and Fig. 1).

Dattagupta (U.S. Patent No. 4,734,363, issued 29 March 1988) teach a method for producing nucleic acids comprising primers having constant and variable domains, extending the primers and separating the nucleic acids (Column 2, line 19-Column 3, line 34 and Fig. 1).

Conclusion

29. No claim is allowed.

30. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (703) 306-5878 until 13 January 2004. Starting 14 January 2004, the examiner's phone number will be (517) 272-0741. The examiner can normally be reached on 6:00 TO 3:30 Monday through Thursday and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone numbers for the organization where this

application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196. Starting 14 January 2003, the receptionist telephone number will be (517)-272-0507.

BJ Forman, Ph.D.
Primary Examiner
Art Unit: 1634
December 18, 2003